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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant(s): Blue, Jeffrey T.

Application Number: 10/030,378

Filing Date: November 9, 2001

Title of the Invention: DETECTION OF VIRAL STABILITY

Examiner: Le, Emily M.

Art Unit: 1648

REPLY BRIEF

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MERCK & CO., INC.

By _____ Date February 28, 2007

Sheldon O. Heber

Response to Examiner's Answer

I. Grounds for Rejection to be Reviewed on Appeal

The Examiner's Answer indicates: (1) the rejection of claims 1-8 and 18-25 under 35 U.S.C. § 112, second paragraph, is withdrawn; (2) the rejection of claims 21 and 24 under 35 U.S.C. § 112, first paragraph (written description), is withdrawn; (3) the rejection of claims 4, 5, 18 and 19 as obvious in based on Banki *et al.* in view of Duncan *et al.*, inadvertently omitted to list claims 21 and 24; and (4) the rejection of claims 1, 20, 23 and 25 inadvertently omitted to list Duncan *et al.* The examiner presents arguments correcting the inadvertent omissions and indicates such arguments are not new rejections. (Examiner's Answer at page 3.)

Appellant appreciates the withdrawal of the U.S.C. § 112 first paragraph and second paragraph rejections. The Examiner's Answer notes that the 35 U.S.C. § 112 first paragraph rejection was not addressed in Appellant's Appeal Brief. The 35 U.S.C. § 112 first paragraph rejection was previously withdrawn in the Advisory Action mailed 06/14/2006, at page 2, first paragraph.

Appellant has no objection to claim 21 being listing in the obviousness rejection to claims 4, 5, 18 and 19. As further discussed below in Argument III.A., claim 21 is argued together with claims 4 and 5.

Appellant objects to claim 24 being listed in the obviousness rejection of the claims 4, 5, 18 and 19. Claim 24 does not appear to have been inadvertently omitted in the obviousness rejection based on Banki *et al.* in view of Duncan *et al.* Claim 24 further describes the virus as either measles or mumps. Neither Duncan *et al.* nor Banki *et al.* are cited by the examiner for describes the virus as either measles or mumps. In the event the Appeal goes forward with claim 24 being part of the rejection, as further discussed below in Argument III.C., claim 24 is argued separately based on reference to the virus being measles or mumps.

Appellant has no objection to Duncan *et al.* being argued by the examiner in the obviousness rejection of claims 1, 20, 23 and 25. For this rejection, the claims continue to be grouped as noted in the Appeal Brief and in Argument VII *infra*.

II. Claims 1-3 and 7 are not Anticipated under 35 U.S.C. § 102(b) by Banki *et al.*

Claims 1-3 and 7 stand rejected as allegedly anticipated by Banki *et al.* (The Journal of Biological Chemistry May, 8, 1998; Vol. 273, No. 19, 11944-11953). The Examiner's Answer refers to different sections in Banki *et al.* argued to provide for: (a) contacting cells susceptible to caspase 3 induction with a virus that induces caspase 3 activity; (b) measuring caspase 3 activity; and (c) repeating steps (a) and (b) at two or more time intervals. The Examiner's Answer also argues that reference in the claim to "provides an indication of virus stability and potency in said first formulation" is not a claim limitation. (Examiner's Answer at pages 4-6.)

A. The Anticipation Rejection Fails to Address Reference in the Claim to the Virus Used to Repeat Steps (a) and (b) Being Taken from a First Formulation at Different Times

Claims 1-3 and 7 incorporate a description of the virus being taken from a first formulation for repeating steps (a) contacting cells susceptible to caspase 3 induction with a virus that induces caspase 3 activity and (b) measuring caspase 3 activity, at two or more time intervals. The rejection argues Banki *et al.* repeats steps (a) and (b) to measure caspase-3 activity at different time intervals and to obtain data in mean standard form. (Examiner's Answer at page 12.)

The rejection fails to identify the formulation used in Banki *et al.* to perform the experiments. Banki *et al.* measures caspase 3 activity to study HIV induced apoptosis. Banki *et al.* describes a continuous time-course for measuring HIV induced apoptosis. The data for the continuous time-course was generated by initially infecting a set of cells, then at different times measuring apoptosis from the initially infected cells.

The rejection appears to argue that the continuous time-course in Banki *et al.* employs a first formulation at different times. In generating data for the continuous time-course, Banki *et al.* does not go back to the first formulation for repeating steps (a) and (b). Instead, Banki *et al.* measures HIV induced apoptosis at different times, where the virus is maintained and is causing apoptosis over time.

While not explicitly stated, or explained in the rejection, the examiner may be referring to a formulation used in Banki *et al.* from which virus was taken to determine the mean variation. However, the rejection fails to point out such a formulation and how it is used in Banki *et al.* The

Patent Office bears the initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Anticipation requires each and every element as set forth in the claim to be described expressly or inherently in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987), *cert. denied,* 484 U.S. 827 (1987).

Banki *et al.* referring to determining the mean variation using four experiments does not necessarily mean that the virus was taken from a first formulation at different times. For example, all four experiments could be performed at the same time using a virus from a particular formulation. An advantage to performing the experiments at the same time is to reduce potential storage effects on the virus, where such effects would interfere with evaluating the effect of HIV on apoptosis.

B. Reference in the Claims to "Provides an Indication of Virus Stability and Potency in said First Formulation"

The examiner refers to *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), noting language in *Minton v. Nat'l Ass'n of Securities Dealer, Inc.* 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003), that a "whereby" clause in a method claim is not given patentable weight when it simply expresses the intended result. (Examiner's Answer at page 6.) Reference in the claims to the phrase "provides an indication of virus stability and potency in said first formulation" relates to the difference in caspase 3 activity and provides a functional limitation. Appellant notes the claims do not use the phrase "whereby".

III. Claims 4, 5, 18, 19, 21 and 24 are Not Obvious Under 35 U.S.C. § 103(a) Based on Banki *et al.* in View of Duncan *et al.*

Claims 4, 5, 18, 19, 21 and 24 stand rejected as allegedly obvious under 35 U.S.C. § 103(a) based on Banki *et al.* in view of Duncan *et al.* (Virology 255, 117-128, 1999). Duncan *et al.* is cited for describing rubella virus inducing apoptosis in Vero and RK13 cells, where Duncan *et al.* quantified the number of detached cells as an indicator of apoptosis. Banki *et al.* is argued by the examiner to provide for measuring activity from a formulation by performing step (a) followed by said step (b) at two or more time intervals. The examiner argues that Duncan *et*

al. is deficient in not teaching measurement of caspase 3 activity and that one skilled in the art would be motivated to combine Banki *et al.* with Duncan *et al.* to quantify viral induced apoptosis using caspase 3 activity. (Examiner's Answer at pages 6 and 7.)

For this rejection, the claims are argued together as follows: (A) claims 4, 5 and 21; (B) claims 18 and 19; and (C) claim 24.

A. Claims 4, 5 and 21

Claims 4, 5, and 21 distinguish the provided rejection, for example, by incorporating a description of: (1) measuring activity from said formulation by performing step (a) contacting cells susceptible to caspase 3 induction with a virus that induces caspase 3 activity and (b) measuring caspase 3 activity, at two or more time intervals using first from a first formulation; and (2) employing either measles, mumps or rubella.

As noted above in Argument II.A. *supra.,* Banki *et al.* fails to necessarily describe performing step (a) followed by said step (b) at two or more time intervals using virus from a first formulation. Duncan *et al.* is not cited for curing the noted deficiencies in Banki *et al.*

Claims 4, 5 and 21 further distinguish Banki *et al.* in view of Duncan *et al.* based on the claim description concerning the virus being either measles, mumps or rubella. Duncan *et al.* teaches measuring apoptosis in general by quantifying detached cells. The examiners proposal to modify Duncan *et al.* to measure caspase 3 activity as indication of viral activity is inconsistent with Duncan *et al.* looking for effects caused by apoptosis in general. A prior art reference must be considered in its entirely including portions teaching way from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock Inc.,* 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed. Cir 1983), *cert. denied,* 469 U.S. 851 (1984).

Duncan *et al.* is not concerned with measuring viral activity. Duncan *et al.* concerns studying the cellular basis of the ability of the rubella virus to cause system birth defects in the fetuses of infected women. (See Duncan *et al.* abstract, first two sentences.) Duncan *et al.* indicates that other caspases, in addition to caspase 3, are involved the observed apoptosis. (Duncan *et al.*, at page 125, first column, third paragraph.)

Given the focus in Duncan *et al.* to look at apoptosis in general, Duncan *et al.* teaches away from looking at caspase 3 activity alone or in combination with other particular caspases as

an indication of viral activity. Banki *et al.* measures caspase 3 activity to study HIV induced apoptosis and does not indicate that such techniques are suitable for studying the cellular basis of the ability of the rubella virus to cause system birth defects in the fetuses of infected women.

B. Claims 18 and 19

Claims 18 and 19 are directed to a method for assaying activity of measles, mumps or rubella by measuring the ability of the virus to induce caspase 3 activity. As noted in Argument VII.A. *supra.*, given the focus in Duncan *et al.* to look at apoptosis in general, Duncan *et al.* teaches away from look at caspase 3 activity alone or in combination with other particular caspases as an indication of viral activity. Banki *et al.* measures caspase 3 activity to study HIV induced apoptosis and does not indicate that such techniques are suitable for studying the cellular basis of the ability of the rubella virus to cause system birth defects in the fetuses of infected women.

C. Claim 24

Claim 24 depends from claim 21, and further distinguishes the combination of Banki *et al.* in combination with Duncan *et al.*, by indicating the virus is either measles or mumps. Banki *et al.* is cited for using HIV and Duncan *et al.* is cited for using rubella. The rejection fails to indicate where the combination of Banki *et al.* and Duncan *et al.* provides for using either measles or mumps.

IV. Claim 6 is Not Obvious 35 U.S.C. § 103(a) Based on Banki *et al.* in View of Wu *et al.*

Claim 6 stands rejected as allegedly obvious under 35 U.S.C. § 103(a) based on Banki *et al.* as applied to claims 1-3, in view of Wu *et al.* (provisional application 60/108606, priority document to U.S. Patent No. 6,689,600). Wu *et al.* is cited for teaching that lyophilization improves stability of viral vaccine and recombinant proteins. (Examiner's Answer pages 7 and 8.)

Claim 6 depends from claim 1. As noted in Argument II.A. *supra.*, claim 1 distinguishes Banki *et al.*, for example, by indicating steps (a) and (b) are repeated at two or more time

intervals using a virus from a first formulation. Wu *et al.* fails to cure such deficiencies in Banki *et al.*

V. Claim 8 is Not Obvious Under 35 U.S.C. § 103(a) Based on Banki *et al.* in View of Goodrich *et al.*

Claim 8 stands rejected as allegedly obvious under 35 U.S.C. § 103(a) based on Banki *et al.* as applied to claims 1-3 in view of Goodrich *et al.* (U.S. Patent No. 5,958,670). Goodrich *et al.* is cited for teaching a method of storing cells by freezing and later thawing. (Examiner's Answer at pages 8 and 9.)

Claim 8 depends from claim 1. As noted in Argument II.A. *supra.* claim 1 distinguishes Banki *et al.*, for example, by indicating steps (a) and (b) are repeated at two or more time intervals using a virus from a first formulation. Goodrich *et al.* fails to cure such deficiencies in Banki *et al.*

VI. Claim 22 is Not Obvious Under 35 U.S.C. § 103(a) Based on Banki *et al.* in View of Esolen *et al.*

Claim 22 further describes the virus of claim 18 as either measles or mumps. Claim 22 stands rejected as allegedly obvious under 35 U.S.C. § 103(a) based on Banki *et al.* in view of Esolen *et al.* (Journal of Virology, June 1995, p. 3955-3958). Banki *et al.* is cited for teaching a method of measuring caspase 3 activity to quantify virally induced apoptosis. Esolen *et al.* is cited for teaching that measles virus induces apoptosis. The examiner argues it would be *prima facie* obvious to combine Banki *et al.* with Esolen *et al.* to quantify apoptosis induced by measles virus. (Examiner's Answer at page 9.)

The skilled artisan would not be motivated to modify Esolen *et al.* using the methods employed by Banki *et al.* to determine the mechanism of measles virus-induced cell death. Esolen *et al.* does not reference caspase 3 activity as involved in the observed cell death or indicate that caspase activity should be quantified. Esolen *et al.* is directed to determining the mechanism of measles virus-induced cell death. (See Esolen *et al.* abstract on page 3955.) In doing so, Esolen *et al.* notes that DNA fragmentation indicative of apoptosis was apparent by flow cytometry, agarose gel electrophoresis and election microscopy. (See Esolen *et al.* Abstract on page 3955.)

VII. Claims 1, 20, 23 and 25 are Not Obvious Under 35 U.S.C. § 103(a) Based on Banki *et al.* in View of Duncan *et al.* and Wu *et al.*

Claims 1, 20, 23 and 25 stand rejected as allegedly obvious under 35 U.S.C. § 103(a) based on Banki *et al.* in view of Duncan *et al.* and Wu *et al.* The rejection is directed to reference in the claims to measurement of caspase 3 activity from two different formulations. Banki *et al.* is cited for teaching a method of measuring caspase 3 activity to quantify viral induced apoptosis. Wu *et al.* is cited for teaching the significance of formulations on biological activity. Duncan *et al.* is cited for describing teaching rubella virus induces apoptosis in Vero and RK13 cells, where Duncan *et al.* quantified the number of detached cells as an indicator of apoptosis. The examiner argues that one of ordinary skill in the art would be motivated to determine the effect of the formulation on the biological activity and structural integrity of the virus. (Examiner's Answer at pages 9 and 10)

For this rejection, the claims are argued as follows: (A) claims 1 and 25; (B) claim 20; and (C) claim 23.

A. Claims 1 and 25

The rejection fails to indicate particular modifications to Banki *et al.* or Wu *et al.* Instead the rejection generally alleges the two references should be combined to provide an assay to determine the effects of a formulation on viral activity. The Patent Office bears the initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker* 977 F.2d at 1445, 24 USPQ2d at 1444.

The fact that formulations can affect viral activity does not provide motivation to measure caspase 3 activity as an indication of viral activity in different formulations. Banki *et al.* concerns studying HIV induced apoptosis. Banki *et al.* does not indicate that caspase 3 activity should be measured to provide an indication of viral activity in comparing different formulations. Wu *et al.* description concerning the significance of formulations on biological activity fails to cure such deficiencies.

The effect of different formulations on viral activity teaches against modifying Banki *et al.* to employ a virus from different formulations. Employing a virus from different formulations, as argued by the examiner, leads to variability in the effect of the virus on HIV induced apoptosis. Depending on the stability of the virus in a particular formulation the virus

could have a decreased potency making it more difficult to interpret the significance of the observed virus effect on apoptosis.

B. Claim 20

As noted in Argument VII.A *supra.*, Banki *et al.,* Wu *et al.,* Duncan *et al.,* fail to provide for measuring viral stability in different formulations. Claim 20 further distinguishes the cited references by indicating the virus is either measles, mumps or rubella.

Banki *et al.* measures caspase 3 activity to study HIV induced apoptosis. Given the focus in Duncan *et al.*, to look at apoptosis in general, Banki *et al.* fails to provide motivation to modify Duncan *et al.* to specifically look at caspase 3 activity alone or in combination with other particular caspases, as an indication of viral activity. Wu is cited for measuring stability and does not cure such a deficiency in Banki *et al.* and Duncan *et al.*

C. Claim 23

As noted in Argument VII.A *supra.*, Banki *et al.,* Wu *et al.,* Duncan *et al.,* fail to provide for measuring viral stability in different formulations. Claim 23 further distinguishes the cited references by indicating the virus is either mumps or rubella. The rejection fails to indicate where the combination of Banki e*t al.* and Duncan *et al.* provides for using either measles or mumps.

CONCLUSION

Appellant requests that the Board of Patent Appeals and Interferences reverse the outstanding rejections of claims 1-8 and 18-25. Please charge deposit account 13-2755 for fees due in connection with this Reply Brief.

Respectfully submitted,

By _____
Sheldon O. Heber
Reg. No. 38,179
Attorney for Appellants

Merck & Co., Inc.
RY60-30
P.O. Box 2000
Rahway, NJ 07065-0907
(732) 594-1958